

# EXHIBIT Z

# Prevention of Periprosthetic Joint Infection

Ramsay Refaie, Simon Jameson and Mike Reed

Periprosthetic joint infection (PJI) can be a catastrophic complication following joint replacement surgery. The financial costs and morbidity associated with PJI are well established<sup>1-3</sup> with evidence now emerging that PJI is an independent risk factor for mortality<sup>4</sup>. Prevention is better than cure and whilst an exhaustive list is beyond the scope of this article we will discuss some offbeat tactics to consider in practice.

## The Basis of the Problem

When Charnley wrote about prosthetic joint infection in 1969 he stated there was "still uncertainty as to how often a wound is infected in the operating room and how often at a later date during the healing of the wound"<sup>5</sup>. This same uncertainty still persists to this day. Contaminants may arise from the patient's skin, from the surgical personnel or from the surgical instrumentation itself<sup>6, 7</sup>. It is likely that almost all surgical wounds are contaminated because skin preparation at the time of surgery will only decontaminate the skin surface and bacteria will remain in deeper layers of the skin<sup>8</sup>. Whilst it is also possible for infection to seed to the implant in haematogenous spread or so called "metastatic infection"<sup>9</sup> this occurs less frequently. Gram-positive organisms are the most commonly reported with *Staphylococcus aureus* accounting for over a third of reported PJIs in England and Wales<sup>10</sup>.

Broadly speaking prevention strategies target modifiable patient factors and peri-operative factors; these are summarised in Table 1. Many of these tactics are presented at open events with The Quality Improvement in Surgical Teams initiative<sup>11</sup>.



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| Risk Factor   | Management   |
|---|--|
| <b>Patient factors</b>  |  |
| Inflammatory arthritis  | <ul style="list-style-type: none"> <li>• Disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate should be discussed with the prescriber</li> <li>• Peri-operative steroids are generally not required</li> <li>• Balance the risks and benefits of stopping anti-TNF – stop at 3-5 half-lives pre-operatively, restart after wound healing and no evidence of infection</li> </ul> |
| Obesity   | <ul style="list-style-type: none"> <li>• Dietician input to encourage weight loss</li> <li>• Adjust peri-operative antibiotic doses appropriately</li> <li>• In super-obese consider bariatric surgery prior to joint replacement surgery</li> </ul>   |
| Smoking   | <ul style="list-style-type: none"> <li>• Consider a smoking cessation programme</li> </ul>   |
| Methicillin Resistant and Methicillin Sensitive <i>Staphylococcus aureus</i> carriage (MRSA and MSSA) | <ul style="list-style-type: none"> <li>• Screening based on local guidelines, and decolonise prior to surgery</li> </ul>   |
| <b>Peri-operative factors</b>   |  |
| Patient preparation   | <ul style="list-style-type: none"> <li>• Shower on day of surgery</li> <li>• If hair removal required, use electric clippers on day of surgery</li> <li>• Avoid oil-based skin moisturisers</li> </ul>   |
| Antibiotics   | <ul style="list-style-type: none"> <li>• Prophylactic antibiotics should be given as early as possible in the anaesthetic room</li> <li>• If cementation is required, antibiotic-impregnated cement should be used</li> <li>• There is little consensus or evidence for which antibiotic prophylaxis</li> </ul>  |
| Theatre   | <ul style="list-style-type: none"> <li>• Use laminar flow where possible</li> <li>• Keep theatre door opening to a minimum</li> </ul>  |
| Personnel   | <ul style="list-style-type: none"> <li>• Hand wash with antiseptic surgical solution, using a single-use brush or pick for the nails</li> <li>• Before subsequent operations hands should be washed with either an alcoholic hand rub or an antiseptic surgical solution</li> <li>• Use scrub staff assisted glove donning</li> <li>• Double glove and change gloves regularly</li> </ul>          |
| Skin preparation  | <ul style="list-style-type: none"> <li>• Use an alcohol pre-wash followed by a 2% chlorhexidine-alcohol scrub solution, or alcoholic betadine. Beware of fires</li> </ul>  |
| Anaesthetic   | <ul style="list-style-type: none"> <li>• Maintain normothermia</li> <li>• Maintain normovolaemia</li> <li>• A higher inspired oxygen concentration peri-operatively and for 6 hours post-operative may be of benefit</li> </ul>  |

**Proven strategies and some food for thought****MSSA screening and decolonisation**

Methicillin Resistant *Staphylococcus aureus* (MRSA) is the emotive “superbug” that every patient seems to fear. Indeed MRSA infections have been shown to have significantly higher treatment costs than other causal organisms of PJI<sup>12</sup>. MRSA screening is now well established across the NHS with positive results prompting decolonisation prior to surgery. However, nasal carriage of Methicillin sensitive organisms (MSSA) also confers an increased risk of PJI. Carriage is common (~20%)<sup>13</sup> and decolonisation presents us with an easy “high yield” strategy in the fight against PJI. A large, randomised, placebo controlled multi-centre trial published in the New England Journal of Medicine in 2010 showed that decolonisation of MSSA carriers with mupirocin nasal ointment and chlorhexidine soap prior to orthopaedic and cardiothoracic surgery reduced their risk of MSSA SSI by almost 60% from 7.7% to 3.4%<sup>13</sup>. This strategy has also been shown to be cost effective<sup>14</sup>. Despite this, many centres still do not routinely screen for MSSA. After MSSA screening and decolonisation was introduced in one NHS joint replacement unit, MSSA infections reduced from 0.84% to 0.26% - the caveat being there were other infection prevention methods implemented during the time period<sup>15</sup>.

**Smoking cessation**

Smokers are at increased risk of wound complications and infections<sup>16</sup>. A randomised controlled trial from Denmark, published in the Lancet, has shown that cessation or at least 50% reduction in smoking decreased wound complications from 31% to

5% ( $p < 0.001$ ) in patients undergoing hip and knee arthroplasty<sup>17</sup>. Smoking cessation should be considered for all patients.

**Patient warming**

Pre warming of patients before theatre is a proven strategy for preventing hypothermia intra-operatively and in recovery<sup>18, 19</sup>. A large RCT from the UK published in the Lancet showed that pre warming reduced the risk of infection by around 65% in clean surgery<sup>20</sup>. Despite this pre warming is still not widely adopted in UK centres.

Intra-operative warming is widely performed but the method of intra-operative patient warming may also alter the risk of infection during clean air surgery<sup>21</sup>. Randomised studies have demonstrated that the popular forced air warming devices interact with laminar air flow currents in such a way that non-filtered air can be drawn from outside the clean air canopy into the wound area<sup>22, 23</sup>. Our own switch to the alternative conductive fabric warming led to a significant decrease in deep infection rates<sup>22</sup>. These concepts are best demonstrated in high definition video ([www.youtube.com/user/orthopodresearch](http://www.youtube.com/user/orthopodresearch)).

**Laminar flow and lights**

Historical evidence has shown that laminar flow in combination with antibiotic prophylaxis reduces infection rates in joint arthroplasty<sup>24</sup>. Recently however, the benefit of laminar flow has come into question<sup>10, 25, 26</sup>.

Given the fragile nature of laminar air flow, we wanted to investigate the impact of popular suspended theatre lights. In a series of experiments using neutrally buoyant helium bubbles we evaluated the efficacy of laminar flow at clearing particles from the operative field looking specifically at the impact of lights. These experiments

**Table 1:** Summary table of common prevention tactics

## JTO Peer-Reviewed Articles

are best viewed in high definition video ([www.youtube.com/user/orthopodresearch](http://www.youtube.com/user/orthopodresearch)). Perhaps unsurprisingly we found that placing lights directly above the operative field impairs the ability of the system to clear airborne particles. Figure 1 shows the rate at which particles were cleared from the operative field after one minute of filling with bubbles. No lights, a single light and two lights over a mannequin knee (Figure 2) were evaluated. This provides further evidence for the intuitive interactions between laminar air flow currents and objects within it. Based on this the lead author has joined several others who operate without suspended theatre lights for knee replacement. Hugh Howorth and Sir John Charnley worked closely to develop the optimal operating environment. The original greenhouse used by Charnley contained two banks of lights to illuminate the operative field<sup>27</sup>. Subsequent Howorth/Charnley theatre designs contained banks of lights outside the laminar flow canopy. The theatre picture of Wrightington Hospital (Figure 3) clearly shows a bank of lights outside the laminar flow enclosure. Whilst this approach is not for everyone, an awareness of the potential interactions with laminar flow and attempts to minimise these should be encouraged.

### Targeted antibiotic prophylaxis

The benefits of prophylactic antibiotics are widely accepted across most surgical specialties<sup>28, 29</sup>. Prophylaxis is however not without risks and the potential reduction in SSIs must be balanced against the adverse effects of antibiotics. Cephalosporins, once a panacea in our prophylactic armamentarium, have fallen out of favour in the UK largely due to their association with *Clostridium difficile* associated diarrhoea (CDAD), despite this representing a relatively minor complication

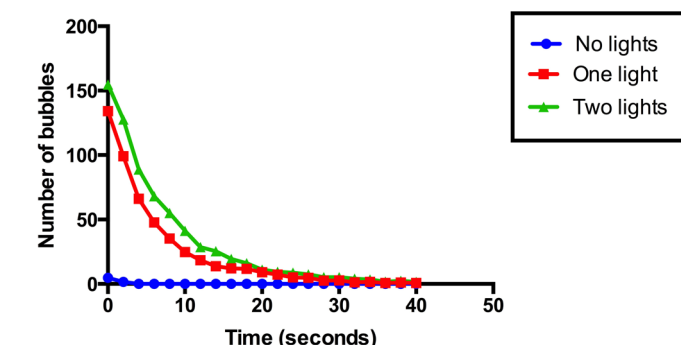


Figure 1: Rate of bubble clearance



Figure 2: Knee mannequin with bubbles being introduced



Figure 3: Old Theatre 1 at Wrightington Hospital

in elective orthopaedic surgery (1.7 per 1000)<sup>30</sup>. A systematic review reported that there is insufficient evidence of a significant difference between cephalosporins, teicoplanin or penicillin derivatives<sup>31</sup>. In practice, most prophylactic regimens are now based on dual therapy yet these are frequently associated

with higher incidence of acute kidney injury and no change in rates of PJI<sup>32-35</sup>. Elsewhere, gentamicin alone has also been shown to offer no benefit in terms of reducing CDAD<sup>36</sup>. With all this confusion a large randomised trial is required to best protect our patients undergoing primary joint replacement.

## Summary

PJI is catastrophic and every feasible step should be taken to prevent this. Whilst this article is not exhaustive it may encourage achievable strategies to reduce the incidence of PJI. ■

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References can be found online at [www.boa.ac.uk/publications/JTO](http://www.boa.ac.uk/publications/JTO) or by scanning the QR Code.







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